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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/626,830 | 07/24/2003 | John Ernest Sims | NWESTERN-08309 | 9231 |

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| EXAMINER | |
|---|---|
| BAUSCH, SARAE L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/626,830 | SIMS ET AL. | |
| | Examiner | Art Unit | |
| | Sarae Bausch | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 11-16* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of group I in the reply filed on 02/15/2006 is acknowledged.

2. During a telephone conversation with Robert Getts on 03/24/2006 a provisional election was made of a specific allele (see page 3, paragraph 2 of the restriction requirement mailed 01/11/2006) with traverse to prosecute the invention of group I, claim 1-2, 11, 14-16 and allele A1,A2 allele combination at an IL1A VNTR intron 6 locus. Affirmation of this election must be made by applicant in replying to this Office action. Claims 12 and 13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### *Claim Rejections - 35 USC § 112- Second Paragraph*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 14-16 provides for the use of hybridization (claim 14), sequencing (claim 15), and mass spectrometry (claim 16), but since the claims does not set forth any steps involved in the method of claim 1 comprising the use of hybridization, sequencing or mass spectrometry, it is unclear what method/process steps applicant is intending to recite in the claimed invention. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

*Claim Rejections - 35 USC § 112- Enablement*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 11, 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to a method of identifying an individual predisposed to early rejection of a kidney allograft comprising a genotype of an IL-1 family member gene wherein the presence of A1, A2 allele combination at an IL1A VNTR intron 6 locus indicates that the individual is at increased risk for early rejection of the kidney allograft. The claims are further drawn to determining the genotype by amplifying a nucleic acid from the IL-1 family

member gene. The claims are further drawn to determining genotyping using hybridization, sequencing, and mass spectrometry.

Guidance in the Specification.

The specification asserts a method for determining whether a subject has or is predisposed to early rejection of a kidney allograft that is associated with an IL-1 family member polymorphism (see page 2, lines 24-26). The specification asserts that the allele associated with increased risk of early kidney allograft rejection can be detected by any of a variety of available techniques including hybridization, sequencing, electrophoretic mobility of an allele (see page 2, lines 32-35). The specification asserts that the nucleic acid to be used for determination of genotype can be obtained from any specimen that contains nucleic acid (see page 5, lines 12-13). However, the specification does not teach a method that is predictably correlative to identification of any individual predisposed to early rejection of kidney allograft by determining the genotype of IL-1A family member gene or the presence of A1,A2 allele combination at IL1A VNTR intron 6 locus.

The specification asserts that a total of 87 kidney allograft recipients were evaluated and 14 patients underwent early rejection of the transplanted kidney. The specification asserts that early rejection of transplanted kidney is defined as rejection within 21 days of transplant (see page 12, lines 6-9). While the specification demonstrates a study of genotyping of patients that had early rejection of transplanted kidney (see table 4, page 16); the specification does not teach a well defined sample and control populations of individuals undergoing kidney allograft and how the presence of the A1, A2 allele combination at IL1A VNTR intron 6 locus correlates with early kidney allograft rejection. The specification does not define the type individuals (humans,

dog, monkey, etc) and how the role of the recited allele varies within or among various animal species. Additionally, the specification does not teach how the health status and how the health of the individual in association with the presence of the recited allele will affect early kidney allograft rejection. The specification does not teach a population study of both a control and sample size that predictably correlates the presence of the A1, A2 allele with an individual with a predisposition to early kidney allograft.

It is unclear from the lack of guidance in the specification how to identify if any individual is predisposed to early rejection of a kidney allograft. The specification only gives limited guidance with respect to detection of specific genotypes of IL-1 family member genes, the specification demonstrates a study of genotyping only IL-1A VNTR, IL-1A +4845, IL-1B +3953, IL-1B –511 and IL-1RN VNTR and does not genotype any other IL-1 family member genes. The specification does not define "rejection" of a kidney allograft. It is unclear based on the teaching in the specification what is encompassed by rejection of a kidney allograft, does rejection encompass complete loss of renal function? Partial renal failure? Pain or swelling of the kidneys? Fever? Any of these symptoms or all of the symptoms? Were the patients each given the same immunosuppression therapy? Were each of the patients genotyped on the same day from receiving the kidney allograft? Were each of the patients on dialysis for the same amount of time? Were other diseases present in the individuals? Were the HLA type , ABO blood composition, alleles of the donor and recipient the same? Different? Health of the individuals prior to graft? The specification only gives limited guidance with respect to the controls used for predictably correlating the presence of the A1, A2 allele in an individuals with early rejection of kidney allograft.

Furthermore, the claims are broadly drawn to "any" individual and the specification only teaches a study of 87 patients, of which 31 were female and 55 were male; 55 were Caucasian, 14 were black, 12 were Hispanic, and 6 were other (see table 1). The specification does not teach a comprehensive study that would predictably correlate if an individual was predisposed to early kidney allograft by detecting A1, A2 allele combination at an VNTR intron 6 locus.

The specification appears to be conceiving of possible scenarios where the genotype could be determined and that these results could indicate increased risk of early rejection of kidney allograft, however, it is unclear how one of skill in the art would determine predictably correlate A1,A2 allele combination at IL1A VNTR intron 6 locus with an increased risk for early rejection of kidney allograft.

Working Examples

The specification demonstrates a working example of determining genotypes of 14 patients that underwent early rejection of transplanted kidney and 73 patients that did not undergo early rejection (see example 1, pages 12-16). The specification demonstrates genotyping analysis was performed using PCR amplification and demonstrate that 6 of the 13 early kidney rejection allograft patients had the A2,A1 IL-1A VNTR genotype and 7 of the 13 patients had a different genotype, while 9 of the 72 patients that did not undergo early kidney rejection allograft had the A2,A1 Il-1A VNTR genotype. It is unclear how the presence of A2,A1 IL-1A VNTR genotype is predictably correlative to an increased risk of early rejection of kidney allograft when not even 50% of the patients that underwent early rejection of the transplanted kidney had the A1, A2 genotype. Furthermore, the specification does not demonstrate if the patient population was administered the same therapy – drug dosage, dialysis, etc. The specification does not

demonstrate a statistically significant study with a proper control study that would correlate any genotype in any IL-1 family gene with an increased risk for early rejection of kidney allograft.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

The unpredictability of the art and the state of the prior art

The prior art teaches that there are many parameters that need to be evaluated prior to using gene expression and genotyping to determine if an individual is at an increased risk for early rejection of kidney allograft.

Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd

column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Pelletier et al. (Transplantation 2000 70 :674-680) teach that there are many clinical variables identified as risk factors for developing acute rejection after renal transplant, which includes delayed graft function, previously allosensitized recipients, high panel reactive antibody recipients, African-American recipients, and poor patient compliance with immunosuppression medication (see last sentence page 677 cont' to page 678). Pelletier et al. teach numerous variables which impact the risk of acute rejection it is unlikely that a variable such as the genetically encoded putative in vivo cytokine production levels could be demonstrated to correlate with acute rejection (see 1st column, 1st paragraph, page 678). Pelletier et al. teach that cytokine gene polymorphisms and posstransplant outcome will vary from center to center due to differences in recipient populations and patient management strategies (see page 678, 2nd column, 2nd full paragraph). Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate A1,A2 allele combination at an IL1A VNTR intron 6 locus with an increased risk for early rejection of kidney allograft.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to correlation of A1,A2 allele combination at IL-1A VNTR intron 6 locus and an individuals increased risk of early rejection of kidney allograft and the lack of guidance with regard to patient population and controls, the quantity of experimentation in this area is extremely large. The skilled artisan would have to determine a predictable correlation between A1,A2 allele combination at IL-1A VNTR intron 6 locus and early rejection of kidney allograft in a population of patients that received the same therapy, with the same graft function, same treatment prior to kidney allograft, and determine the patient compliance with immunosuppression medication. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine genotypes of IL-1A intron 6 in many different populations and first determine if genotype is present prior to rejection of kidney allograft. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if the genotyping of IL-1A intron 6 is in fact detecting rejection of kidney allograft. There is still a significant amount of unpredictably in genotypes of individuals and a skilled artisan after detection of the sequence would have to perform a large exhaustive assay to test for genotype detection in large study pool to determine the specific genotype would predictably correlate an increased risk of early rejection of kidney allograft in individuals. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the lack of guidance on how to predictably correlate genotype of IL-1A intron 6 locus, much less any IL-1 family member gene with an increased risk for early rejection of

kidney allograft, the large quantity of research required to define the lack of guidance provided in the specification, the absence of working examples, and the negative teaching in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make the claimed invention.

***Conclusion***

7. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Sarae Bausch, PhD.
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER